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(54) Title: A PROLONGED RELEASE COMPOSITION, USE AND PRODUCTION THEREOF

(57) Abstract

A composition containing a crosslinked product derived from a water-soluble polysaccharide and biologically active ingredient, preferably, microcapsules retaining a biologically active ingredient in the crosslinked product derived from a water-soluble polysaccharide, in which a biologically active ingredient is incorporated in a high efficiency, and the composition has an excellent prolonged release effect, the composition of this invention can be prepared by a convenient and safe manner without necessity of using an organic solvent. Furthermore, by allowing one of the biologically active ingredients which are incompatible to one another to be enclosed in microcapsules, a mixed composition containing these biologically active ingredients can be provided by using the composition of this invention.

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DESCRIPTION

A PROLONGED RELEASE COMPOSITION, USE AND PRODUCTION THEREOF

Technical field

This invention relates to a composition which comprises a biologically active ingredient and a crosslinked product derived from a water-soluble polysaccharide, more specifically, a microcapsule retaining at least one species of biologically active ingredients in the crosslinked product derived from water-soluble polysaccharide, to a method of preparing same, and to use of the crosslinked products.

Background Art

Various investigations have been conducted on the attempt of making a drug to release slowly from a composition and allowing the effect of the drug thus released to continue for a desired period of time. Among them, studies on microcapsules prepared by allowing a drug to be incorporated in a high molecular polymer have been extensively conducted. For example, a method of preparing sustained-release microcapsules referring to cure-coating method in a liquid system using W/O type emulsion (J. Pharm. Pharmacol. 1993, 45: 16-20). This method has such drawbacks as low incorporation efficiency of a water-soluble drug into microcapsules and requiring a large amount of investment, when the method is carried out on an industrial scale, for securing safety to human health and the living environment or taking measures for preventing explosion due to the use of an organic solvent to remove fluid paraffin.

On the other hand, as the method of preparing microcapsules of a water-soluble drug, "drying method in liquid system" is known well ["New Technique of Microencapsulation and Development of its Use:Application Examples" Management Development

Center, 10. Sept. S53(1978)]. This method includes O/O type, W/O/W type and O/W type, which is accompanied with such drawbacks, namely; O/O type requires the use of a large volume of a solvent, W/O/W type requires repetition of emulsifying process twice although the the volume of solvent used is smaller than that in O/O type and the process is complicated, and, although O/W type required smaller volume of solvent to be used as compared with the foregoing two methods, distribution of a water-soluble drug into the aqueous phase is prone to occur, thus the amount of a drug to be incorporated is extremely small.

And in JPA H5(1993)-85902, there is disclosed a method of preparing a sustained-release agricultural chemical by liquefying an effective component and a bio-degradable polymer having an aliphatic polyester linkage together with an organic solvent capable of dissolving this polymer and by owing the liquid material to be retained on a mineral type carrier. In this method also an organic solvent is employed, and it is required to take measures for securing safety of human health or the living environment and preventing explosion.

Further, a method of preparing matrix prepared by cross-linking gelatine containing a drug with glutaraldehyde and its effects are disclosed [J. Controlled Release, 31(1994), 255-261]. This method comprises complicated steps, i.e. preparing gelatin gel containing a drug, drying the gel, then immersing the dried gel in a glutaraldehyde solution to occur cross-linking reaction, washing the cross-linked product with water, followed by drying to obtain the matrix.

As described above, conventional techniques preparing microcapsules have such disadvantages, i.e. complicated steps, use of an organic solvent undesirable for human health and the living environment

or difficulty in allowing a water-soluble drug to be incorporated in microcapsules simply and conveniently with good efficiency.

Circumstances being such as above, development of microcapsules, which can be prepared conveniently without using an organic solvent and with high drug-incorporation into the microcapsule, has been desired.

The object of this invention is to provide a composition, which comprises a biologically active ingredient and, a crosslinked product derived from a water-soluble polysaccharide, more specifically, a microcapsule retaining at least one species of a biologically active ingredients in the crosslinked product derived from a water-soluble polysaccharide, whose ability of intaking the biologically active ingredient is improved, a use of the crosslinked product and a method of preparing same.

Disclosure of Invention

For solving the above-mentioned problems, the present inventors have diligently conducted extensive study and succeeded in preparing a microcapsule retaining at least one species of biologically active substance in a crosslinked product derived from a water-soluble polysaccharide by subjecting water-soluble polysaccharide to crosslinking with aldehyde, using acid chloride as the catalyst for crosslinking in water, and then by subjecting the crosslinked product to spray-drying. This method, which does not require the use of an organic solvent, can be conducted simply, conveniently and safely.

And, the present inventors found that, while the present method is the one conducted in an aqueous system, water-soluble biologically active substance can be incorporated in the microcapsule at unexpectedly high efficiency, and, beside, the release of the biologically active substance can be optionally

controlled.

Further, the present inventors found that, by using this microcapsule, a mixed composition, in which the incorporated ingredients exert no undesirable effects to one another and decomposition of the ingredients as the agricultural chemicals is suppressed, can be produced.

Based on these findings, the present inventors have conducted further study to accomplish the present invention.

More specifically, the present invention provides;

(1) a composition, which comprises a biologicalyl active ingredient, and a crosslinked product derived from a water-soluble polysaccharide,

(2) a composition according to (1) which is a microcapsule,

(3) a composition according to (1) or (2), wherein the crosslinked product derived from a water-soluble polysaccharide is water-slightly-soluble or water-insoluble,

(4) a composition according to (1), (2) or (3), wherein the water-soluble polysaccharide is a water-soluble natural polysaccharide polymer or a water-soluble semi-synthetic polysaccharide polymer,

(5) a composition according to (4), wherein the water-soluble natural polysaccharide polymer is starch; dextrin; cyclodextrin; mannan or polysaccharide produced by seaweed, plant or microorganism.,

(6) a composition according to (5), wherein the starch is rice starch, sweet potato starch, potato starch, tapioca starch, wheat starch or corn starch; the cyclodextrin is α -, β - or γ -cyclodextrin; the mannan is konjak mannan; the polysaccharide produced by seaweed is funori (a glue plant), agar or sodium arginate; the polysaccharide is Hibiscus manihot, tragacanth gum or arabic gum,

(7) a composition according to (4), wherein the water-soluble semi-synthetic polysaccharide polymer is a water-soluble semi-synthetic polymer derived from cellulose or a water-soluble semi-synthetic polymer derived from starch,

(8) a composition according to (7), wherein the water-soluble semi-synthetic polymer derived from cellulose is viscose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, a salt of carboxymethyl cellulose, hydroxypropyl cellulose or hydroxypropylmethyl cellulose; the water-soluble semi-synthetic polymer derived from starch is solubillized starch, carboxymethyl starch, dialdehyde starch, dextrin derivative, cyclodextrin derivative, oxidized starch, etherified starch, esterified starch or amylose,

(9) a composition according to any one of (1) to (8), wherein the crossliked product is derived by crosslinking a water-soluble polysaccharide with glutaraldehyde, formaldehyde, glyoxal, epichlorohydrin or dialdehyde starch,

(10) a composition according to (1), wherein the biologically active ingredient is an insecticidal ingredient,

(11) a composition according to (1), wherein the biologically active ingredient is a herbicidal ingredient,

(12) a composition according to (1), wherein the biologically active ingredient is a fertilizer,

(13) a composition according to (10), wherein the insecticidal ingredient is Cartap hydrochloride,

(14) a composition according to (10), wherein the insecticidal ingredient is 1-(2-chloro-5-thiazolylmethyl)-3-methyl-2-nitroguanidine,

(15) a composition according to (11), wherein the herbicidal ingredient is 1-(2-chloroimidazo[1,2-

a]pyridin-3-ylsulfonyl)-3-(4,6-dimethoxypyrimidin-2-yl)urea,

(16) a composition according to (2), wherein the microcapsule contains about 0.1 to 80 weight % of a biologically active ingredient relative to the whole weight of the microcapsule,

(17) a composition according to (2), wherein the microcapsule contains about 1 to 99.9 weight % of a crosslinked product derived from a water-soluble polysaccharide relative to the whole weight of the microcapsule,

(18) a microcapsule, which is produced by;

i) dissolving or suspending a biologically active ingredient and a crosslinking agent in an aqueous solution of a water-soluble polysaccaride to give a mixture;

ii) subjecting the mixture to carry a crosslinking reaction under existence of a catalyst for a crosslinking reaction to give a reaction mixture; and

iii) spray-drying the reaction mixture,

(19) a method for producing a microcapsule, which comprises;

i) dissolving or suspending a biologically active ingredient and a cross liking agent in an aqueous solution of a water-soluble polysaccaride to give a mixture;

ii) subjecting the mixture to carry a crosslinking reaction under existence of a catalyst for a crosslinking reaction to give a reaction mixture; and

iii) spray-drying the reaction mixture,

(20) a agricultural, pharmaceutical or fertilizal composition, which comprises a microcapsule of (2) and a suitable carrier,

(21) a composition according to (20), which contains a microcapsule of claim 2, at least a biologically active ingredient which is incompatible to the biologically

active ingredient in the microcapsule and a suitable carrier, and

(22) use of a crosslinked product derived from a water-soluble polysaccharide for prolonged releasing biological active ingredient from a composition.

More specifically, the present invention provides;

(23) the composition according to (1) characterized by containing about 1 to 80, preferably about 10 to 60 weight % of a biologically active ingredient, relative to the total weight of the composition,

(24) the composition according to (1) characterized by containing about 20 to 90, preferably about 40 to 90 weight % of a crosslinked product derived from water-soluble polysaccharide with a cross-linking agent, relative to the total wieght of the composition,

(25) the composition according to (1), wherein the molecular weight of the watersoluble polysaccharide is about 1000 to 200,000,

(26) the composition according to (1), wherein the watersoluble polysaccharide is methyl cellulose,

(27) the composition according to (1), wherein the ingredient is a water-soluble, water-insoluble or hardly water-soluble agriculturally active or pharmaceutically active ingredient,

(28) the microcapsule according to (2), containing about 0.1 to 80, preferably about 10 to 80, more preferably about 10 to 60 weight % of a biologically active ingredient and about 1 to 90 weight % of a water-soluble polysaccharide and about 1 to 90 weight % of a crosslinking agent, relative to the total wight of the microcapsule,

(29) a method of preparing the microcapsule according to (19) wherein the weight ratio of the biologically active ingredient to the water-soluble polysaccharide is about 1:100 to about 10:1, preferably about 1:100 to about 5:1, the weight ratio of the water-soluble

polysaccharide to the crosslinking agent is about 100:1 to about 1:10, and the weight ratio of the crosslinking agent to the catalyst for crosslinking reaction is about 100:1 to about 1:10,

(30) the composition according to (20) further containing an additive employable for an agricultural chemical or medicinal composition,

(31) the composition according to (30), wherein the additive is a surfactant, carrier, anti-oxidant, dispersant, fluid material, preservative, synergist, emulsifier, suspending agent, spreading agent, penetrating agent, wetting agent, mucilage, stabilizer, sticking agent or adsorbent,

(32) the composition according to (20), which is characterized by containing about 0.1 to 70 weight % of microcapsules relative to the total weight of the composition,

(33) the composition according to (20), which is characterized by containing about 0.1 to 80, preferably about 0.1 to 70, more preferably about 10 to 60 weight % of at least one species of biologically active ingredients which are incompatible with the biologically active ingredients retained in the microcapsule, relative to the total weight of the composition, and

(34) the composition according to (14), which is in the form of granule, dust or tablet.

The biologically active ingredient employable for the composition of this invention can be selected from a broad field of, covering not only pharmaceutically active substances and agriculturally active substances but also fertilizers. These biologically active substances may be water-soluble, water-insoluble or hardly water-soluble ones. The biologically active substances employable for the composition of this invention are exemplified in the following, but they

are not limited to them.

S or O after the name of these drugs means respectively solid substances or oily ones at room temperatures (about 1 to 30°C).

(1) Agriculturally active substance

[carbamate type insecticides]:

PHL, propoxur:S; MIPC, isoprocarb:S; BPMC, fenobucarb:S; MPMC, xylylcarb:S; MTMC, metolcarb:S; XMC (S), ethiofencarb:S; NAC carbaryl:S, pirimicarb:S; bendiocarb:S; carbofuran:S; furathiocarb:O; carbosulfan:O; aminosulfulan; methomil:S; cartap:S; fenoxycarb:S; alanycarb:S; chloethocarb:S; benfuracarb:O; and fenothiocarb:S.

[Organic phosphor type insecticides]:

MPP, fenthion:O; MEP, fenitrothion:O; propaphos:O; cyanophos:O; prothiophos:O; sulprofos:O; profenofos:O; EPN (O); cyanofenphos:S; acephate:S; oxydeprofos:O; disulfoton:O; thiometon:O, phenthoate:S; malathion:O; dimethoate:S; vamidothion:S; mecarbam:O; DEP, trichlorphon:S; naled:O; dichlorvos:O; chlorofenvinphos:O; CVMP, tetrachlorvinphos:S; monocrotophos:S; phosalone:S; dialifos:S; chlorpyrifosmethyl:S; chlorpyrifos:S; pirimiphosmethyl:O; diazinon:O; etrimfos:O; pyridaphenthion:S; quinalphos:S; isoxathion:S; DMTP. methidathion:S; salithion:S; pyraclophos:O; chlorthiophos:O; fortress:O; isofenphos:O; butathiofos; and EDDP (O).

[Pyrethroid type insecticides]:

cyfluthrin:O; permethrin:O; cypermethrin:S; deltamethrin:S; cyhalothrin:O; fenpropathrin:S; flucythrinate:O; fulbalinate:O; ethofenprox:S; silanophane; fenpropathrin:S; tralomethrin:S; cycloprothrin:O; acrinathrin:S; and resmethrin:S.

[Urea type insecticides]:

difulbenzuron:S; chlorfluazuron:S; nomolto:S;

hexaflumuron:S; fluf noxuron:S; diafenthiuron:S; flucycloxuron:S; and hexythiazox:S.

[Other insecticides]:

thiocyclam:S; buprofezin:S; bensultap:S; imidacloprid:S; hydroprene:S; fenazaquin:O; clofentezine:S; levamisol:S; dienochlor:S; cyromazine:S; fenpyroximate:S; pyridaben:S; pyriproxyfen:S; sulfluramid:S; thiodicarb:S; nitenpyram:S; 1-(2-chloro-5-thiazolylmethyl)-3-methyl-2-nitroguanidine; endosulfan:S; flufenoxuron:S; diflubenzuron:S; and chlorfluazuron:S.

[Carbamate type fungicides]:

zineb:S; maneb:S; benomyl:S; thiophanate-methyl:S; cypendazole:S; carbendazin:S; prothiocarb:S; and diethofencarb:S.

[Antibiotic type fungicides]:

validamycin A:S; kasugamycin:S; avermectin:S; milbemycin:S; and mildiomycin:S.

[Anilide type fungicides]:

mepronil:S; flutolanil:S; pencycuron:S; carboxin:S; oxycarboxin:S; pyracarbolid:O; mebenil:S; furcarbanil; cyclafuramid:S; benodanil:S; granovax; metalaxyl:S; ofurace:S; benalaxyl:S; oxadixyl:S; cyprofuram:S; clozylacon; metsulfovax; and tecloftalam:S.

[Organic phosphor type fungicides]:

edifenphos:O; IBP(O); pyrazophos:S; aliette; and tolclophos-methyl:S.

[Azole type fungicides]:

fenarimol:S; flurprimidol:S; fluotrimazole:S; triadimefon:S; triadimenole:S; dichlobutrazol:S; paclobutazol:S; diniconazole:S; uniconazole:S; triflumizole:S; propiconazole:O; flutriafol:S; flusilazole:S; penconazole:S; prochloraz:O; triapenthenol:S; triarimol:S; fenarimol:S; bitertanol:S; imazalil:O; etaconazol :S; paclobutrazol:S; phenapronil; viniconazole;

difenoconazole:S; bromuconazole:S; myclobutanil:S; hexaconazole:S; cyproconazole:S; furconazole-cis:S; fenethanil; and tebuconazole.

[Dicarboxyimide type fungicides]:

dichlozoline:S; iprodione:S; vinclozoline:S; procymidone:S; myclozolin; and fluoroimide:S.

[Other fungicides]

fthalide:S; (trade name) monguard:S; isoprothiolane:S; tricyclazole:S; probenazole:S; ferimzone:S; fluazinam:S; butiobate:O; pyroquilon:S; chlobenchiazone; TPN, chlorothalonil:S; captan:S; captafol:S; folpet:S; thiabendazole:S; fuberidazole:S; tridemorph:O; fenpropimorph:O; triforine:S; ethirimol:S; dimethirimol:S; hymexazol:S; ethazol:O; fenpropidin:O; pyrifenox:O; dimethomorph:S; fenpiclonil:S; zariamid; triclamide:S; flusulfamide:S; befran:S; dimefluazole; oxolinic acid:S; proxychlor; dichlomezin:S; and anilazine:S.

[Pheromone]:

okimeranolure:S; cherrytlure:O; and daimolure:O.

[Insecticides and fungicides other than those mentioned above]:

fipronil:S; novaluron; flufenprox; fenpyrad or tebufenpyrad:S; methoxadiazone; benfluthrin; pyriproxyfen:S; diafenthiuron:S; dichlorfluanid:S; ftalaxyl; flapenazole; pipanipirim; thicyofen; (trade name) opus:S; ipconazole:S; dimetconazole; myxothiazol; thioimiconazole; and quinconazole.

[Herbicides]:

imazosulfuron:S; N-(2-ethylsulfonylimidazo[1,2-a]pyridin-3-ylsulfonyl)-N'-(4,6-dimethoxy-2-pyrimidinyl)urea:S; dimethametryn:S; dymron:S; atrazine:S; cyanazine:S; ametryne:S; alachlor:S; butachlor:O; metolalchlor:O; IPC (S); CIPC (S); thiobencarb:O; butylate:O; EPTC (O); dicamba:S; monuron:S; diuron:S; fluometuron:S; chloroxuron:S;

benzthiazuron:S; karbutilate:S; metoxurin:S; methabenzthiazuron:S; chlorotoluron:S; isoproturon:S; trifluralin:S; pendimethalin:S; 2,4-D (S); MCPA (S); MCPP (S); molinate:O; epronaz:S; sethoxydim:O, alloxydim:S; tralkoxydim:S; fluazifop-butyl:O; quizalofop-ethyl:S; fenxaprop-ethyl:S; haloxyfop ethoxyethyl:S; fluazifop-P-butyl:O; framprof-M-isopropyl; tridiphane:S; methazole:S; oxadiazon:S; bentazone:S; pyrazolate:S; chlormethoxynil:S; chlornitrofen:S; dichlofop-methyl; oxyfluorfen:S; lactofen:O; achronifen:S; propanil:S; metribuzin:S; acyfluorfen:S; fomesafen:S; bensulfuron methyl:S; chlosulfuron:S; chlorimuron methyl:S; primisulfuron-methyl:S; triasulfuron:S; imazaquin:S; imazamethabenz:S; imazethapyr:S; tribenuron methyl:S; benzoylpropethyl:S; difenzoquat:S; ioxynil:S; bifenox:S; clopyralid:S; mecoprop:S; metsulfuron-methyl:S; fluroxypyr:S; isoxaben:S; thiameturon-methyl:S; fluoroglycofen-ethyl:S; bromoxynil:S; pendimethalin:S; prometryn:S; pyrazosulfuron-ethyl:S; piperophos:O; esprocarb:O; pyributicarb:O; dithipyr:S; HW-52(2',3'-dichloro-4-ethoxymethoxybenzanilide:S); benzofenap:S; benoxazol:O; bromobutide:S; chlomeprop; chlorthiamid:S; dalapon:O; dimepiperate:S; fluothiuron:S; chlornitrofen:S; MCPB (S); MCPCA; mefenacet:S; methoxypenone:S; naproanilide:S; nitrofen:S; phenopylate:O; pyrazoxyfen:S; simetryn:S; swep:S; and cinosulfuron.

Among the active components as mentioned above, those which are in solid state at room temperatures can be treated, after dissolving in, for example, a solvent of a high boiling point, in a similar manner to that for oily components.

(2) Pharmaceutically active substance

[Antibiotics] tetracycline hydrochloride, ampicillin and piperacillin.

[Antipyretics.analgesics.antiphlogistics]
sodium salicylate, sulpyrine, indomethacin sodium and morphine hydrochloride.
[Antitussives.expectorants]
ephedrine hydrochloride, noscapine hydrochloride, codeine phosphate, dihydrocodeine phosphate and isoproterenol hydrochloride.
[Sedatives]
chlorpromazine and atropine sulfate.
[Anti-ulcer agents]
metachlobromide and histidine hydrochloride.
[Antiarrhythmic agents]
propranolol hydrochloride and alprenolol hydrochloride.
[Antihypertensive, diuretic agents]
hexamethonium bromide and chronizine hydrochloride.
[Anticoagulants]
heparin sodium, sodium citrate.
(3) Fertilizers
[Nitrogenous fertilizers]
ammonium sulfate, ammonium nitrate, ammonium phosphate, calcium nitrate, urea.
[Phosphatic fertilizer]
ammonium phosphate, ammonium sulfate-phosphate, bone powder.
[Potassic fertilizer]
potassium chloride, potassium sulfate.

In the composition of this invention, one or more species of the above-mentioned active substances can be employed.

As water-soluble polysaccharides employable in the present invention, those having a molecular weight of about 1000 to 200,000 are preferable, those having a molecular weight of about 2000 to 100,000 are more preferable. The water-soluble polysaccharides are, exemplified by polysaccharides of water-soluble natural polymer or water-soluble semi-synthetic polymer.

The term "water-soluble" means that about 0.01 g or more, preferably about 0.1 g or more of the polysaccharide can be dissolved in 100 ml of water at 25°C.

Examples of the water-soluble natural polymer include starch, dextrin, cyclodextrin, mannan, polysaccharide produced by seaweed, plant and microorganism.

More specifically, starch is exemplified by rice starch, sweet-potato starch, potato starch, tapioca starch, wheat starch and corn starch. As cyclodextrin is examplified by α-, β- or γ-cyclodextrin. As mannan, mention is made of, for example, konjak mannan. As polysaccharides produced by seaweed, mention is made of, for example, funori (a glue plant), agar and sodium alginate. As polysccharides produced by plant, mention is made of, for example, Hibiscus manihot, tragacanth gum and acacia.

As water-soluble semi-synthetic polymer, mention is made of, for example, cellulose type water-soluble semi-synthetic polymer and starch type water-soluble semi-synthetic polymer. As the cellulose-type ones, mention is made of, for example, viscose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, a carboxymethyl cellulose salt, hydroxypropyl cellulose or hydroxypropylmethyl cellulose, and the starch-type water-soluble semi-synthetic polymer is soluble starch, carboxymethyl starch, dialdehyde starch, dextrin derivative, cyclodextrin derivative, oxidized starch, etherified starch, esterified starch or amylose. Among them, cellulose type ones are preferable, specifically methyl cellulose, for example, is preferable.

Methyl cellulose means, generally, methyl ether of cellulose. In the glucose residue of cellulose, there are one primary alcohol group and two secondary alcohol

groups, and they are substituted in the form of methyl ether. In this case, while it is said that primary alcohol is easier to be substituted, methoxyl groups are distributed variously. Methyl cellulose to be employed in the present invention may be any ones only when they are water-soluble, and then can be used in admixture with any of the above-mentioned water-soluble polysaccharides. In general, the output of polysaccharides of natural water-soluble polymer changes largely depending on climate, thus stable supply of them being relatively difficult. On the other hand, as the supply of polysaccharides of water-soluble semi-synthetic polymer is stable, use of them is more preferable.

As the crosslinking agent to be employed for the composition of this invention, any one can be used if only it is capable of crosslinking water-soluble polysaccharides, which is exemplified by an aldehyde compound. More specifically, glutaraldehyde, formaldehyde, glyoxal, epichlorohydrin and dialdehyde starch, for example, are preferable.

The crosslinked product derived from a water-soluble polysaccharide, which is used for the composition of this invention, can be obtained by subjecting the water-soluble polysaccharide and the crosslinking agent to crosslinkage by a per se known method using a catalyst for the crosslinking reaction. For example, a water-soluble polysaccharide is mixed with an aqueous solution of a crosslinking agent (an aldehyde compound e.g. formaldehyde, glyoxal or glutaraldehyde). To the mixture is added, while stirring, a catalyst for the crosslinking reaction (e.g. acid chloride such as benzoyl chloride, propionyl chloride, acetyl chloride) to allow the crosslinking reaction to proceed, thereby the object crosslinked material is produced. The reaction time ranges usually

from about 30 minutes to about 3 hours, preferably from about 30 minutes to about one hour. The reaction temperature ranges usually from room temperature to 60°C, preferably from about 10 to 60°C, more preferably usually from about 20 to 40°C.

Preferable examples of a catalyst for the crosslinking reaction include alkanoyl chloride such as benzoyl chloride, propionyl chloride.

The ratio of a water-soluble polysaccharide and a crosslinking agent in the crosslinking reaction ranges usually from about 100:1 to about 1:10, preferably from about 10:1 to about 1:5 by weight.

The ratio of a crosslinking agent and a catalyst for the crosslinking reaction ranges usually from about 100:1 to about 1:10, preferably from about 5:1 to about 1:5 by weight.

The content of drugs in the composition of this invention ranges usually from about 0.1 to 80 weight %, preferably from about 1 to 80 weight %, more preferably usually from about 10 to 60 weight %, relative to the total weight of the composition.

The content of the crosslinked product derived from a water-soluble polysaccharide in the composition of this invention ranges usually from about 1 to 99.9 weight %, preferably from about 20 to 95 weight %, more preferably usually about 40 to 90 weight %.

The crosslinked product derived from water-soluble polysaccharide, which is obtained by the above-mentioned crosslinking reaction, can be used as it is or as granules prepared by drying and crushing the material.

By employing a crosslinked product derived from a water-soluble polysaccharide in the composition of this invention, biologically active ingredient can be retained stably and the release of the ingredient can be controlled. Therefore, the composition of this

invention is useful as a prolonged release composition having the ingredient incorporated stably. Further, since the crosslinked product derived from of a water-soluble polysaccharide is biodegraded in natural environment or in living bodies, it can be used as a safe additive to agricultural, pharmaceutical or fertilizal compositions.

It is further possible to incorporate such additives as conventionally employable for agricultural, pharmaceutical or fertilizal compositions into the composition of this invention.

In the case where the composition of this invention is an agricultural chemical composition, as additives, use is made of, for example, a surfactant, carrier (e.g. diluent, filler), anti-oxidant (e.g. dibutyl hydroxy toluene, 4,4-thiobis-6-tert-butyl-3-methylphenol), dispersant (e.g. ethylene glycol, glycerine), fluidizing aid (e.g. white carbon), preservative (e.g. sorbic acid potassium sorbate, methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butyl p-hydroxybenzoate, benzoic acid and salicylic acid), synergist, emulsifier, suspending agent, spreading agent, penetrating agent, wetting agent, mucilage, stabilizer, sticking agent or adsorbent.

As the surfactant, use is made of cationic, anionic or nonionic one, singly or in admixture of two more of them. Among them, a nonionic surfactant is preferable. Practically, surfactants such as polyoxyethylene alkylaryl ethers [e.g. Noigen™, E.A 142™; manufactured by Dai-Ichi kôgyô Seiyaku Co., Ltd., Nonâl™; manufactured by Toho Chemical Industry Co., Ltd.], alkyl sulfates [e.g. Emal 10™, Emal 40™; manufactured by Kaô Co., Ltd.], alkylsulfonates [e.g. Neogen™, Neogen T™; Dai-Ichi Kôgyô Seiyaku Co., Ltd., Neoperex™; manufactured by Kaô Co., Ltd.],

polyethyl ne glycol ethers [e.g. Nonipol 85™, Nonipol 100™, Nonipol 160™: manufactured by Sanyo Ch mical Industries, Ltd.] and polyhydric alcohol esters [e.g. Tween 20™, Tween 80™; manufactured by Kaô Co. Ltd.] are used as occasion may demand.

As the carrier, use is made of, for example, a diluent or filler of a solid carrier. As the solid carrier, use is made of, for example, vegetable powder (e.g. soybean powder, tabacco powder, wheat powder and wood powder), mineral powder (e.g. clay such as kaolin, bentonite and acid clay, talc such as talc powder and pagodite, and silica such as diatomaceous earth and mica powder), alumina, sulfur powder, activated charcoal and calcium carbonate, which can be used singly or in admixture of two or more of them in a suitable ratio.

The amount of these additives to be employed ranges usually from about 0.01 to 99.9 weight %, preferably from about 30 to 99.9 weight %, more preferably from 40 to 99.5 weight %. Practically, in the case of using a surfactant, the amount ranges usually from about 0.2 to 20 weight %, preferably from about 0.2 to 10 weight %. In the case of a carrier, the amount ranges usually from about 1 to 99.9 weight %, preferably from about 20 to 99.5 weight %. In the case of an antioxidant, the amount ranges usually from about 0.02 to 0.2 weight %, preferably from about 0.02 to 0.1 weight %. In the case of a fluidizing aid, the amount ranges usually from about 0.1 to 5 weight %, preferably from about 0.1 to 3 weight %. In the case of a preservative, the amount ranges usually from 0.05 to 0.3 weight %, preferably from about 0.05 to 0.2 weight %.

In the case where the composition of this invention is an agricultural composition, the above-mentioned components can be formed into various

preparations such as microcapsule, dust, tablet or granule in accordance with a per se known method generally employed for preparation of agricultural chemical compositions or an analogous method thereto.

The agricultural composition of this invention can be used by conventional methods, while varying with, e.g. kinds of the active components or the noxious insects, including, for example, processing with a box of raising seedlings, sprinkling over stalks and leaves of plants, sprinkling over insects, scattering in water of paddy field or mixing with the soil.

While the amount of the agricultural composition of this invention to be used varies broadly with the time, place and method, it is generally selected so as the amount of the agriculturally active ingredient to fall into ranges, from about 1 to 500 g, preferably from about 5 to 200 g, per 10 are.

In the case where the composition of this invention is a fertilizal composition, the same additives mentioned in the agricultural composition can be employed.

The fertilizal composition of this invention can be used by conventional method, while varying with, e.g. kinds of the fertilizers or the plants.

While the amount of the fertilizal composition of this invention to be used varies broadly with the time, place and method, it is generally selected so as the amount of the fertilizer to fall into the range from 1 to 1000g, preferably from 10 to 700g, per 10 are.

In the case where the composition of this invention is a pharmaceutical composition, it can be prepared by a conventional means to be employed for the preparation of conventional medicinal compositions. The pharmaceutical composition can be used orally as, depending on necessity, sugar-coated tablet, capsule, elixir or microcapsule, or non-orally in the form of

injection of a sterile solution or suspension in water or any other pharmaceutically acceptable solvent.

For example, the pharmaceutical composition can be prepared by mixing active components, in the unit dosage form required for preparing pharmaceuticals generally admitted, with e.g. a physiologically acceptable carrier, flavoring agent, vehicle, preservative, stabilizer and binder. The amount of active components in the composition should be within the range then desired. As the additives to be mixed in, e.g. tablets or capsules, use is made of, for example, a binder such as gelatin, corn starch, tragacanth or acacia, an excipient such as crystalline cellulose, a swelling agent such as corn starch, gelatin or alginic acid, a lubricant such as magnesium stearate, a sweetener such as sucrose, maltose or saccharine, and a flavouring agent such as peppermint, acamono oil or cherry. In the case where the preparation unit form is capsule, the composition may contain, besides the above-mentioned type materials, a liquid carrier. The sterile composition for injection can be prescribed by conventional formulation, for example, by making a mixture of an active substance in a vehicle such as water for injection and a natural vegetable oil such as seasame oil or coconut oil into a solution or suspension.

As the injectable aqueous solution, mention is made of an isotonic solution (e.g. D-sorbitol, D-mannitol and sodium chloride) containing an adjuvant such as a physiological aqueous saline solution or glucose, and a suitable solubilizer such as alcohol (e.g. ethanol), polyalcohol (e.g. propylene glycol and polyethylene glycol), a nonionic surfactant (e.g. polysorbate 80™ and HCO-50™) can be used combinedly. As the oily liquid, mention is made of, for example, seasame oil or soybean oil, and, as the solubilizer,

use is made of, for example, benzyl benzoate and benzyl alcohol combinedly. Besides, a buffering agent (e.g. a phosphate buffer solution or a sodium acetate buffering solution), a soothing agent (e.g. benzalkonium chloride or procaine hydrochloride), a stabilizer (e.g. human serum albumin or polyethylene glycol), a preservative (e.g. benzyl alcohol or phenol), an antioxidant or the like may be incorporated. Thus-prepared injectable solution is usually filled in an adequate ampoule.

The pharmaceutical composition of this invention thus obtained is low in toxicity and can be administered safely to, for example, warm-blooded mammals (e.g. rat, mouse, chicken, rabbit, sheep, swine, cow, cat, dog, monkey, sacred baboon, chimpanzee and man).

While the amount of the pharmaceutical composition of this invention varies with subjects to be administered, symptoms or the like, it ranges, in the case of oral administration, usually from about 0.1 to 100 mg in terms of the drug component per day per adult (about 60 kg body weight), preferably from about 1.0 to 50 mg, more preferably from about 1.0 to 20 mg. In the case of non-oral administration, while the dosage varies with subjects to be administered, organs to be subjected, symptoms, administration methods or the like, it is convenient that, in the case of injection for example, about 0.01 to 30 mg, preferably about 0.1 to 20 mg, more preferably about 0.1 to 10 mg is usually administered to an adult (60 kg) per day intravenously. In the case of other animals, the amount calculated in terms of that for 60 kg of body weight can be administered.

The composition of this invention can be used, by preparing into microcapsules among the above-mentioned formulations, as prolonged release microcapsule improved in incorporation efficiency of biologically

active ingredients.

In other words, the present invention provides a microcapsule retaining at least one species of biologically active ingredients in a crosslinked product derived from a water-soluble polysaccharide.

As the biologically active ingredients, water-soluble polysaccharides, crosslinking agents and catalysts for the crosslinking reaction, use is made of such ones as described above, and the amounts of them to be employed can be selected in such manners as described above.

The microcapsule of this invention can be produced by dissolving or suspending a biologically active substance and a crosslinking agent in an aqueous solution of a water-soluble polysaccharide, adding thereto a catalyst for the crosslinking reaction to allow the reaction to proceed, then by subjecting the reaction product to spray-drying.

Practical preparation of the microcapsule comprises the following steps.

(1) Preparation of the aqueous solution of suspension containing a water-soluble polysaccharide and a biologically active ingredient:

A biologically active substance is added to an aqueous solution of a water-soluble polysaccharide, and the mixture is stirred to prepare the aqueous solution or suspension. As the stirrer, use is made of, for example, a homomixer, a three one motor, DYNO-MILL™ (Willy A. Bachofen AG Mashinenfabric, Germany) and a Microfluidizer™.

When the biologically active substance is water-soluble one, the substance itself is dissolved in an aqueous solution of a water-soluble polysaccharide to make an aqueous solution. When the biologically active substnace is water-insoluble or hardly soluble in water, the substance itself is suspended, or, after

crushing into powder of about 0.1 to 20 μm, preferably about 0.2 to 10 in average particle size, then by dispersing homogeneously in the aqueous solution of an aqueous solution of a polysaccharide to make a suspension. Or, the particle size of the biologically active substance is relatively large, the substance itself is suspended in an aqueous solution of a polysaccharide, then the suspension may be subjected to wet grinding.

In this case, the volume of water is adequately selected depending on the kinds of water-soluble polysaccharides or biologically active substances. Usually, the concentration of a water-soluble polysaccharide is within the range of about 0.1% to 60% (W/W), preferably 0.5 to 30%.

(2) Crosslinking reaction:

With the solution prepared in (1) above is mixed the aqueous solution of a crosslinking agent (e.g. an aldehyde compound such as formaldehyde, glyoxal and glutaraldehyde). To the mixture is added, while stirring, a catalyst for the crosslinking reaction to allow the reaction to proceed. The reaction time ranges usually from about 30 minutes to 3 hours, preferably from about 30 minutes to one hour. The reaction temperature ranges usually from room temperature to 60°C, preferably from about 10 to 60°C, more preferably usually from about 20 to 40°C.

And, by changing the amounts or ratios of the water-soluble polysaccharide and the crosslinking agent, the network structure of the microcapsule can be controlled, and, as the result, release of the drug can be controlled. Therefore, in order to attain desired effect of sustained-release, the amounts or ratios of a water-soluble polysaccharide or a crosslinking agent can be appropriately selected. For example, increase of the ratio of a crosslinking agent serves to improve

the prolonged release effect. Practically, taking the microcapsule of cartap hydrochloride as an example, in cases where the ratios of a water-soluble polysaccharide and a cross-linking agent are set as 10:2 (W:W), 10:3 (W:W) and 10:4 (W:W), respectively, the release of cartap hydrochloride after one month is 59.9%, 45.3% and 35.6%, respectively.

(3) Drying of the reaction mixture:

The reaction mixture prepared by (2) above is dried by spray-drying usually at temperatures ranging from about 50 to 150°C. While the number of rotations of atomizer in a spray-dryer varies with the kinds of machines. In the case of employing, for example, the spray-dryer-L-8 type (manufactured by Oogawara Kakoki), drying at the conditions of about 30,000 rpm and 15 ml/min. flux gives usually microcapsules of about 5 to 100 μm.

Further, other than the above-mentioned components, any desirable additives can be incorporated into the microcapsules of this invention. For example, in order to suppress the biodegradation of saccharides, a preservative (e.g. sorbic acid, 4-chloro-3,5-xylenol, butyl para-hydroxybenzoate and salicylic acid) is employed.

These other additives can be incorporated in such concentrations as not disturbing the activity of biologically active ingredient and the prolonged release effect. These additives can be incorporated into microcapsules by adding to the aqueous solution or suspension containing a water-soluble polysaccharide and biologically active ingredient in the above step (1).

By preparation process described above, although it is the process of preparing microcapsule in the aqueous syst m not using an organic solvent, a large amount of biologically active ingredient can be

incorporated into the microcapsule. The microcapsule of this invention prepared by the above-mentioned process has about 5 to 500 μm, preferably about 5 to 300 μm, especially preferably about 50 to 200 μm of the diameter in its dry particle.

While the content of each component of the microcapsule of this invention can be selected similarly to that of the above-mentioned composition, it is more preferably as follows.

The amount of biologically active ingredient to be employed in the microcapsule of this invention ranges usually from about 0.1 to 80 weight %, preferably from about 1 to 80 weight %, more preferably from about 10 to 60 weight % relative to the total weight of the microcapsule.

The content of the crosslinked product derived from an water-soluble polysaccharide in the microcapsule of this invention ranges usually from about 1 to 99.9 weight %, preferably from about 20 to 99.9 weight %, more preferably from about 40 to 90 weight % relative to the total weight of the microcapsule.

The content of a water-soluble polysaccharide of the microcapsule of this invention ranges usually from about 1 to 90 weight %, preferably from about 20 to 90 weight %.

The content of the crosslinked product in the microcapsule of this invention ranges usually from about 1 to 90 weight %, preferably from about 20 to 90 weight %.

In the microcapsule of this invention, a large amount of biologically active ingredient is incorporated, and since the microscapsule has an excellent sustained-release property, effects of the biologically active ingredient can be efficiently displayed continuously. Further, since safe and less

toxic components are employed in the microcapsule of this invention, in the case where the biologically active ingredient contained are, for example, agriculturally active ingredient, the microcapsule can be used as a safe and less toxic prolonged release agricultural composition, and, in the case where the biologically active ingredient contained are medicines, the microcapsule can be used as a safe and less toxic prolonged release pharmaceutical composition, further in the case where the biologically active ingredient is a fertilizer, the microcapsule can be used as a safe and effective prolonged release fertilizal composition.

The method of using the microcapsule of this invention varies with, among others, the kinds of biologically active ingredients contained. For example, in the case where the biologically active ingredient is an agricaltural ingredient, a pharmaceutically ingredient or a fertilizer, the composition of this invention can be used the above-mentioned method.

While the microcapsule of this invention can be used solely by itself, it can be used as an agricultural, fertilizal or pharmaceutical composition containing the microcapsule of this invention, by mixing, in accordance with a conventional method, the microcapsule of this invention with, when desired, one or more kinds of biologically active ingredient other than those contained in the microcapsule of this invention or (and) an additive employable for agricultural chemical or pharmaceutical compositions. The microcapsule can be formulated into various preparations, for example, powdery preparations, tablets and granules, by, for example, mixing with or allowing to be adsorbed on an adequate carrier, then by subjecting the mixture to a per se known method or an analogous method thereto generally employed for the

preparation of agricultural chemical or pharmaceutical compositions.

As biologically active ingredient other than the biologically active ingredient contained in the microcapsule, which are employable for the agricultural, fertilizal or pharmaceutical composition containing the microcapsule of this invention (hereinafter sometimes abbreviated as "microcapsule-containing composition"), use is made of those adequately selected from the biologically active ingredients described above. Especially, as biologically active ingredients other than those contained in the microcapsule, use is desirably made of one or more kinds of biologically active ingredients which are incompatible with the biologically active ingredients contained in the microcapsule. In other words, by allowing one of the biologically active ingredients which are incompatible with each other to be incorporated into the microcapsule of this invention, a mixed pharmaceutical preparation containing drugs, which are incompatible with each other, can be provided.

To put it concretely, as combinations of the biologically active ingredient (A) allowed to be contained in the microcapsule and the biologically active ingredient (B) which is incompatible with the biologically active ingredient contained in the microcapsule, mention is made of the following.

(1) (A) nitenpyram and (B) cartap hydrochloride, bensultap or fenitrothion

(2) (A) cartap hydrochloride and (B) nitenpyram, ferimzone or methomil

(3) (A) acephate and (B) ferimzone or methomil

(4) (A) ferimzone and (B) cartap hydrochloride, fenitrothion or acephate

(5) (A) fenitrothion and (B) nitenpyram, bensultap,

ferimzone or tricyclazole

(6) (A) bensultap and (B) nitepyram, BPMC or fenitrothion

The content of the biologically active ingredient, which is incompatible with the biologically active ingredient contained in the microcapsule, in the microcapsule-containing composition of this invention ranges usually from about 0.1 to 80 weight %, preferably from about 0.1 to 70 weight %, more preferably from about 10 to 60 weight %.

It is possible to incorporate such additives as conventionally employable for agricultural, fertilizal or pharmaceutical compositions into the microcapsule-containing composition of this invention.

In the case where the microcapsule-containing composition of this invention is an agricultural composition, as additives, use is made of, for example, a surfactant, carrier (e.g. diluent, filler), anti-oxidant (e.g. dibutyl hydroxy toluene, 4,4-thiobis-6-tert-butyl-3-methylphenol), dispersant (e.g. ethylene glycol, glycerine), fluidizing aid (e.g. white carbon), preservative (e.g. sorbic acid potassium sorbate, methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butyl p-hydroxybenzoate, benzoic acid and salicylic acid), synergist, emulsifier, suspending agent, spreading agent, penetrating agent, wetting agent, mucilage, stabilizer, sticking agent or adsorbent.

As the surfactant, use is made of cationic, anionic or nonionic one, singly or in admixture of two more of them. Among them, a nonionic surfactant is preferable. Practically, surfactants such as polyoxyethylene alkylaryl ethers [e.g. Noigen (trade name), E.A 142 (trade name); manufactured by Dai-Ichi kôgyô Seiyaku Co., Ltd., Nonâl (trade name); manufactured by Toho Chemical Industry Co., Ltd.],

alkyl sulfates [e.g. Emal 10 (trade name), Emal 40 (trade name); manufactured by Kaô Co., Ltd.], alkylsulfonates [e.g. Neogen (trade name), Neogen T (trade name); Dai-Ichi Kôgyô Seiyaku Co., Ltd., Neoperex; manufactured by Kaô Co., Ltd.], polyethylene glycol ethers [e.g. Nonipol 85 (trade name), Nonipol 100 (trade name), Nonipol 160 (trade name); manufactured by Sanyo Chemical Industries, Ltd.] and polyhydric alcohol esters [e.g. Tween 20 (trade name, Tween 80 (trade name); manufactured by Kaô Co., Ltd.] are used as occasion may demand.

As the carrier, use is made of, for example, a diluent or filler of a solid carrier. As the solid carrier, use is made of, for example, vegetable powder (e.g. soybean powder, tabacco powder, wheat powder and wood powder), mineral powder (e.g. clay such as kaolin, bentonite and acid clay, talc such as talc powder and pagodite, and silica such as diatomaceous earth and mica powder), alumina, sulfur powder, activated charcoal and calcium carbonate, which can be used singly or in admixture of two or more of them in a suitable ratio.

The amount of microcapsules used in the microcapsule-containing composition of this invention usually ranges, relative to the total weight of the composition, from about 0.1 to 70 weight%, preferably from about 0.1 to 40 weight %, more preferably from about 0.5 to 30 weight %.

The amount of biologically active ingredients other than those contained in the microcapsule, in the microcapsule-containing composition of this invention, ranges usually, relative to the total weight of the composition, from about 0.1 to 70 weight %, preferably from about 0.1 to 30 weight %, more preferably from about 0.1 to 20 weight %.

The amount of these additives to be employed in

the microcapsule-containing composition of this invention ranges usually from about 0.01 to 99.9 weight %, preferably from about 30 to 99.9 weight %, more preferably from 40 to 99.5 weight %. Practically, in the case of using a surfactant, the amount ranges usually from about 0.2 to 20 weight %, preferably from about 0.2 to 10 weight %. In the case of a carrier, the amount ranges usually from about 1 to 99.9 weight %, preferably from about 20 to 99.5 weight %. In the case of an antioxidant, the amount ranges usually from about 0.02 to 0.2 weight %, preferably from about 0.02 to 0.1 weight %. In the case of a fluidizing aid, the amount ranges usually from about 0.1 to 5 weight %, preferably from about 0.1 to 3 weight %. In the case of a preservative, the amount ranges usually from 0.05 to 0.3 weight %, preferably from about 0.05 to 0.2 weight %.

In the case where the microcapsule-containing composition of this invention is an agricultural or a fertilizal composition, the above-mentioned components can be formed into various preparations such as microcapsule, dust, tablet or granule in accordance with a per se known method generally employed for preparation of agricultural chemical compositions or an analogous method thereto.

The microcapsule-containing agricultural or fertilizal composition of this invention can be used by conventional methods, while varying with, e.g. kinds of the active ingredients or the noxious insects, including, for example, processing with a box of raising seedlings, sprinkling over stalks and leaves of plants, sprinkling over insects, scattering in water of paddy field or mixing with the soil. The amount of the composition is the same as the above-mentioned amount.

In the case where the microcapsule-containing composition of this invention is a pharmaceutical

composition, it can be prepared by a conventional means to be employed for the preparation of conventional medicinal compositions. The pharmaceutical composition can be used orally as, depending on necessity, sugar-coated tablet, capsule, elixir or microcapsule, or non-orally in the form of injection of a sterile solution or suspension in water or any other pharmaceutically acceptable solvent.

For example, the pharmaceutical composition can be prepared by mixing active components in a unit dosage form generally admitted in the pharmaceutical preparation with e.g. a physiologically acceptable carrier, flavoring agent, vehicle, preservative, stabilizer and binder. The amount of active components in these compositions should be within the range then desired. As the additives to be mixed in, e.g. tablets or capsules, use is made of, for example, a binder such as gelatin, corn starch, tragacanth or acacia, an excipient such as crystalline cellulose, a swelling agent such as corn starch, gelatin or alginic acid, a lubricant such as magnesium stearate, a sweetener such as sucrose, maltose or saccharine, and a flavouring agent such as peppermint, acamono oil or cherry. In the case where the formulation unit dosage is capsule, the composition may contain, besides the above-mentioned type materials, a liquid carrier. The sterile composition for injection can be prescribed by conventional formulation, for example, by making a mixture of an active substance in a vehicle such as water for injection and a natural vegetable oil such as seasame oil or coconut oil into a solution or suspension.

As the injectable aqueous solution, mention is made of an isotonic solution (e.g. D-sorbitol, D-mannitol and sodium chloride) containing an adjuvant such as a physiological aqueous saline solution or

glucose, and a suitable solubilizer such as alcohol (e.g. ethanol), polyalcohol (e.g. propylene glycol and polyethylene glycol), a nonionic surfactant (e.g. polysorbate 80 (TN) and HCO-50) can be used combinedly. As the oily liquid, mention is made of, for example, seasame oil or soybean oil; and, as the solubilizer, use is made of, for example, benzyl benzoate and benzyl alcohol combinedly. Besides, a buffering agent (e.g. a phosphate buffer solution or a sodium acetate buffering solution), a soothing agent (e.g. benzalkonium chloride or procaine hydrochloride), a stabilizer (e.g. human serum albumin or polyethylene glycol), a preservative (e.g. benzyl alcohol or phenol), an antioxidant or the like may be incorporated. Thus-prepared injectable solution is usually filled in an adequate ampoule.

The pharmaceutical composition of this invention thus obtained is low in toxicity and can be administered safely to, for example, warm-blooded mammals (e.g. rat, mouse, chicken, rabbit, sheep, swine, cow, cat, dog, monkey, sacred baboon, chimpanzee and man).

The amount of the pharmaceutical composition of this invention is the same as the above-mentioned amount.

Best Mode for Carrying Out of the Invention

Examples

The following Working Examples, Reference Examples and Test Examples are intended to illustrate this invention in detail and should by no means be construed as limiting the scope of the invention to them.

Working Example 1 Padan·Microcapsule (1)

In 1000 ml of a 5% aqueous solution of methyl cellulose were dissolved 51.2 g of cartap and 144 ml of a 25% aqueous solution of glutaraldehyde. The mixture was stirred with a homomixer. To this solution was added dropwise 100 ml of benzoyl chloride, and the

mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 500 ml of water. This solution was subjected to spray-drying under conditions of inlet temperature 100°C, outlet temperature 50°C and number of revolutions of atomizer 30,000 rpm/min. to afford microcapsules as a powdery product.

Working Example 2 Padan-Microcapsule (2)

In 1000 ml of a 5% aqueous solution of methyl cellulose were dissolved 10.2 g of cartap hydrochloride and 54 ml of a 25% aqueous solution of glutaraldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 37.5 ml of benzoyl chloride, and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 500 ml of water. This solution was subjected to spray-drying under conditions of inlet temperature 100°C, outlet temperature 50°C and number of revolutions of atomizer 30,000 rpm/min. to afford microcapsules as a powdery product.

Working Example 3 Padan-Microcapsule (3)

In 250 ml of a 10% aqueous solution of hydroxypropyl cellulose (HPC; HPC EF-P™, Shin-Etsu Chemical Co. Ltd., Japan) were dissolved 62.1 g of cartap hydrochloride and 125 ml of a 25% aqueous solution of glutaraldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 85 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 500 ml of water. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 4 Padan-Microcapsule (4)

In 500 ml of a 5% aqueous solution of

hydroxypropyl cellulose (HPC; HPC EF-P™, Shin-Etsu Chemical Co. Ltd., Japan) were dissolved 62.1 g of cartap hydrochloride and 125 ml of a 25% aqueous solution of glutaraldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 85 ml of benzoyl chloride, and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 600 ml of water. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 5 Padan-Microcapsule (5)

In 833 ml of a 3% aqueous solution of hydroxypropyl cellulose (HPC; HPC EF-P™, Shin-Etsu Chemical Co. Ltd., Japan) were dissolved 62.1 g of cartap hydrochloride and 125 ml of a 25% aqueous solution of glutaraldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 85 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 6 Padan-Microcapsule (6)

In 500 ml of a 5% aqueous solution of hydroxyethyl cellulose (HEC; HEC™, Wako Pure chemical Industries Ltd., Japan) were dissolved 62.2 g of cartap hydrochloride and 125 ml of a 25% aqueous solution of glutaraldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 85 ml of benzoyl chloride, and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 270 ml of water. This solution was subjected to spray-drying under condition of inlet temperature

100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 7 Padan-Microcapsule (7)

In 500 ml of a 5% aqueous solution of hydroxyethyl cellulose (HEC; HEC™, Wako Pure chemical Industries Ltd., Japan) were dissolved 95.2 g of cartap hydrochloride and 165 ml of a 25% aqueous solution of glutaraldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 85 ml of benzoyl chloride, and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 200 ml of water. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 8 Padan-Microcapsule (8)

In 500 ml of a 5% aqueous solution of hydroxyethyl cellulose (HEC; HEC™, Wako Pure chemical Industries Ltd., Japan) were dissolved 62.2 g of cartap hydrochloride and 125 ml of a 25% aqueous solution of glutaraldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 85 ml of propionyl chloride, and the mixture was stirred for 40 minutes at room temperature. To the reaction mixture was added 500 ml of water. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 9 Padan-Microcapsule (9)

In 500 ml of a 5% aqueous solution of hydroxyethyl cellulose (HEC; HEC™, Wako Pure chemical Industries Ltd., Japan) were dissolved 95.2 g of cartap hydrochloride and 165 ml of a 37% aqueous solution of

formaldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 85 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 500 ml of water. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 10 Padan-Microcapsule (10)

In 250 ml of a 10% aqueous solution of Toyoderin P™ (Asahi Foods Co. Ltd., containing 50% of cyclodextrins, specially 30% of α-cyclodextrin) were dissolved 25.6 g of cartap hydrochloride and 82 ml of a 37% aqueous solution of formaldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 42 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 11 Padan-Microcapsule (11)

In 250 ml of a 10% aqueous solution of Toyoderin P™ (Asahi Foods Co. Ltd.) were dissolved 19 g of cartap hydrochloride and 16.5 ml of a 37% aqueous solution of formaldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 8.5 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 12 Padan-Microcapsule (12)

In 250 ml of a 10% aqueous solution of Toyoderin

P™ (Asahi Foods Co. Ltd.) were dissolved 15.9 g of cartap hydrochloride and 27.5 ml of a 37% aqueous solution of formaldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 14.2 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 13

In 97.8 g of water was dispersed 12.2 g of 1-(2-chloro-5-thiazolylmethyl)-3-methyl-2-nitroguanidine and this mixture was shattered with DYNO MILL™ (batch-type, 3 min.). The mill was washed with 95.1 g of water. To the combined aqueous suspension (150 g) were added 25 g of Toyoderin P™ (Asahi Foods Co. Ltd., Japan) and 120 ml of a 37% aqueous solution of formaldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 60 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 14

In 95.1 g of water was dispersed 14.9 g of 1-(2-chloro-5-thiazolylmethyl)-3-methyl-2-nitroguanidine and this mixture was shattered with DYNO MILL™ (batch-type, 3 min.). The mill was washed with 410 g of water. To the combined aqueous suspension (485 g) were added 25 g of hydroxyethyl cellulose (HEC; HEC™, Wako Pure Chemical Industries Ltd., Japan) and 165 ml of a 37% aqueous solution of formaldehyde. The mixture was stirred with a homomixer. To the solution was added

dropwise 85 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 600 ml of water. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 15

In 400 ml of a 15% aqueous solution of Toyoderin P™ (Asahi Foods Co. Ltd., Japan) were dissolved 22.3 g of 1-[N-(6-chloro-3-pyridyl)methyl-N-ethyl]amino-1-methylamino-2-nitroethylene and 72 ml of a 37% aqueous solution of formaldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 36 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outlet temperature 50°C and number of revolution of atomizer 30,000 rpm/min. to give powdery microcapsules.

Working Example 16

In 96.5 g of water was dispersed 13.5 g of 1-(2-chloroimidazo[1,2-a]pyridin-3-ylsulfonyl)-3-(4,6-dimethoxypryidin-2-yl)urea and this mixture was shattered with DYNO MILL™ (batch-type, 3 min.). The mill was washed with 175 g of water. To the combined aqueous suspension (250 g) were added 25 g of Toyoderin™ (Asahi Foods Co. Ltd., Japan) and 35 ml of a 37% aqueous solution of formaldehyde. The mixture was stirred with a homomixer. To the solution was added dropwise 85 ml of propionyl chloride, and the mixture was stirred for 30 minutes at room temperature. To the reaction mixture was added 600 ml of water. This solution was subjected to spray-drying under condition of inlet temperature 100°C, outl t temperature 50°C and number of revolution of atomizer

30,000 rpm/min. to give powdery microcapsules.

Working Example 17 Padan granules

A mixture of 11.3 weight parts of microcapsules prepared in Working Example 1 (4.0 weight parts of cartap hydrochloride), 2.5 weight parts of α starch, 0.5 weight parts of PAP auxiliary, 1.5 weight part of 85% phosphoric acid, 0.5 weight part of a surfactant (NP-85™) and 82.7 weight parts of clay for granulation was kneaded by a kneader, to which was added water, and the mixture was further kneaded. Thus kneaded material was subjected to extrusion granulation (ϕ 1 mm), followed by sizing, drying and sieving (#10 to #48) to obtain granules.

Working Example 18 Padan granules

A mixture of 23.5 weight parts of the microcapsules obtained in Working Example 2 (cartap hydrochloride 4.0 weight parts), 3.5 weight % of α starch, 0.5 weight part of PAP auxiliary, 1.5 weight part of 85% phosphoric acid, 0.5 weight parts of s surfactant (NP-85) and 70.5 weight parts of clay for granulation was kneaded by a kneader, to which was added water, and the mixture was further kneaded. Thus kneaded material was subjected to extrusion granulation (ϕ 1 mm)m followed by sizing, drying and sieving (#10 to #48) to obtain granules.

Working Example 19

A mixture of 14.3 weight parts of microcapsules produced in Working Examples 3 to 9 (4.0 weight parts of cartap hydrochloride), 3.5 weight parts of α-starch, 0.5 weight parts of PAP auxiliary, 1.5 weight parts of 85% phosphoric acid, 0.5 weight parts of surfactant (NP-85) and 78.7 weight parts of clay for granulation was kneaded by a kneader, to which was added water, and the mixture was further kneaded. The resulting mixture was subjected to extrusion granulation (ϕ 1 mm), followed by sizing, drying and sieving (#10 to #48) to

give granules.

Working Example 20

A mixture of 23.8 weight parts of microcapsules produced in Working Example 10 to 12 (6.5 weight parts of cartap hydrochloride), 3.5 weight parts of α-starch, 0.5 weight parts of PAP auxiliary, 1.5 weight parts of 85% phosphoric acid, 0.5 weight parts of surfactant (NP-85) and 70.2 weight parts of clay for granulation was kneaded by a kneader, to which was added water, and the mixture was further kneaded. The resulting mixture was subjected to extrusion granulation (ϕ a mm), followed by sizing, drying and sieving (#10 to #48) to give granules.

Reference Example 1

In 9.75 g of a 20% aqueous solution of polyvinyl alcohol were dissolved 0.398 g of cartap hydrochloride and 0.4 ml of a 25% aqueous solution of glutaraldehyde. The solution was emulsified in 100 ml of fluid paraffin containing 0.05 g of dioctyl sulfosuccinate. To the emulsion was added dropwise, while stirring at 30°C, 1.8 ml of benzoyl chloride. The mixture was stirred for further 30 minutes to give relatively hard microcapsules. The microcapsules were washed with petroleum ether or haxane on a glass filter to eliminate fluid paraffin. The microcapsules were dried, washed with a 0.01N aqueous solution of hydrochloric acid and dried at 30°C to give microcapsules.

Reference Example 2 Padan granules

A mixture of 4.0 weight parts of cartap hydrochloride, 3.5 weight parts of α starch, 0.5 weight part of PAP auxiliary, 1.5 weight part of 85% phosphoric acid, 0.5 weight part of a surfactant (NP-85) and 90.0 weight parts of clay for granulation was kneaded by a kneader, to which was added water, and the mixture was further kneaded. The kneaded material was

subjected to extrusion granulation (φ 1 mm), followed by sizing, drying and sieving to give granules.

Test Example 1 Test method of incorporation efficiency

To about 500 mg of the microcapsules obtained in Working Example 2 placed in a round-bottom flask was added 50 ml of a 1% aqueous solution of hydrochloric acid. The mixture was refluxed for one hour on an oil bath of about 120°C. The reaction mixture was left standing for cooling, which was subjected to ultrasonic cleaning for 15 minutes. The resultant was subjected to filtration. Then the content of cartap hydrochloride was determined in accordance with the method described in "official assay method of agricultural chemicals" to determine its incorporation efficiency. The incorporation efficiency shown in Table 1 is shown by (the amount actually incorporated / theoretical content) x 100 (%).

The incorporation efficiency of cartap hydrochloride in the microcapsules prepared by Reference Example 1 was determined in accordance with the method described in "official assay method of agricultural chemicals", namely, the cartap hydrochloride leaked into the fluid paraffin and the organic solvent used for washing was subjected to extraction with a 0.01 N aqueous solution of hydrochloric acid, which was subjected, in the same manner as in the case of a 0.01N aqueous solution of hydrochloric acid used for washing, to the determination.

The incorporation efficiency shown in [Table 1] is shown by [theoretical content-(actual amount leaked into fluid paraffin + organic solvent used for washing + 0.01N aqueous solution of hydrochloric acid used for washing)].

Table 1

Incorporation efficiency of cartap hydrochloride

Sample	Incorporation efficiency (%)
Working Example 2	96.3
Reference Example 1	68.6

From Table 1, it was found that a large amount of padan was incorporated in the padan·microcapsule of this invention.

Test Example 2 Release test method

In 100 ml of a 0.01 N aqueous solution of hydrochloric acid put in a glass vessel was dispersed homogeneously a sample weighed accurately. After the lapse of a given time, a portion of the solution was taken, which was subjected to determination of the amount of released cartap hydrochloride by the method described in "Official assay method of agricultural chemicals". The released rate in Table 2 was shown by (amount actually released/theoretical amount x 100 (5)).

Table 2

Releasability of cartap hydrochloride from granules

Sample	1 min. (%)	6 hr. (%)	1 day (%)	one week (%)	one month (%)
W.Ex.3	-	14.8	17.7	27.6	32.8
W.Ex.4	-	22.8	22.8	33.6	49.5
R.Ex.2	97.6	100.0	100.0	100.0	100.0

From Table 2, it was found that Padan granules of this invention had excellent sustained-release effects.

Industrial Applicability

The composition of this invention containing a crosslinked product derived from a water-soluble polysaccharide can retain a biologically active ingredient stably in the composition. And, the release of the ingredient from the composition can be

controlled. Especially, the microcapsule of this invention can incorporate even a water-soluble biologically active ingredient in a high efficiency. And, in the granules containing the microcapsules of this invention, release of the ingredient is prolonged, thus the granules are effective as sustained-release compositions capable of showing the ingredient effects for a long period of time. Furthermore, by using the microcapsules of this invention, a composition, in which ingredients which are incompatible with one another are contained, can be provided.

Besides, the method of preparing the microcapsules of this invention does not require the use of an organic solvent, and, despite the method being the one conducted in aqueous system, a relatively large amount of drugs can be incorporated into the microcapsules.

CLAIMS

What is claimed is:

1. A composition, which comprises a biologically active ingredient and a crosslinked product derived from a water-soluble polysaccharide.

2. A composition according to claim 1 which is a microcapsule.

3. A composition according to claim 1, wherein the crosslinked product derived from a water-soluble polysaccharide is water-slightly-soluble or water-insoluble.

4. A composition according to claim 1, 2 or 3, wherein the water-soluble polysaccharide is a water-soluble natural polysaccharide polymer or a water-soluble semi-synthetic polysaccharide polymer.

5. A composition according to claim 4, wherein the water-soluble natural polysaccharide polymer is starch; dextrin; cyclodextrin; mannan or polysaccharide produced by seaweed, plant or microorganism.

6. A composition according to claim 5, wherein the starch is rice starch, sweet potato starch, potato starch, tapioca starch, wheat starch or corn starch; the cyclodextrin is α -, β - γ -cyclodextrin; the mannan is konjak mannan; the polysaccharide produced by seaweed is funori (a glue plant), agar or sodium arginate; the polysaccharide is Hibiscus manihot, tragacanth gum or arabic gum.

7. A composition according to claim 4, wherein the water-soluble semi-synthetic polysaccharide polymer is a water-soluble semi-synthetic polymer derived from cellulose or a water-soluble semi-synthetic polymer derived from starch.

8. A composition according to claim 7, wherein the water-soluble semi-synthetic polymer derived from cellulose is viscose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, a salt of

carboxymethyl cellulose, hydroxypropyl cellulose or hydroxypropylmethyl cellulose; the water-soluble semi-synthetic polymer derived from starch is solubillized starch, carboxymethyl starch, dialdehyde starch, dextrin derivative, cyclodextrin derivative, oxidized starch, etherified starch, esterified starch or amylose.

9. A composition according to any one of claims 1 to 8, wherein the crosslinked product is derived by cross liking a water-soluble polysaccharide with glutaraldehyde, formaldehyde, glyoxal, epichlorohydrin or dialdehyde starch.

10. A composition according to claim 1, wherein the biologically active ingredient is an insecticidal ingredient.

11. A composition according to claim 1, wherein the biologically active ingredient is a herbicidal ingredient.

12. A composition according to claim 1, wherein the biologically active ingredient is a fertilizer.

13. A composition according to claim 10, wherein the insecticidal ingredient is Cartap hydrochloride.

14. A composition according to claim 10, wherein the insecticidal ingredient is 1-(2-chloro-5-thiazolylmethyl)-3-methyl-2-nitroguanidine.

15. A composition according to claim 11, wherein the herbicidal ingredient is 1-(2-chloroimidazo[1,2-a]pyridin-3-ylsulfonyl)-3-(4,6-dimethoxypyrimidin-2-yl)urea.

16. A composition according to claim 2, wherein the microcapsule contains about 0.1 to 80 weight % of a biologically active ingredient relative to the whole weight of the microcapsule.

17. A composition according to claim 2, wherein the microcapsule contains about 1 to 99.9 weight % of a crosslinked product derived from a water-soluble

polysaccharide relative to the whole weight of the microcapsule.

18. A microcapsule, which is obtained by;

i) dissolving or suspending a biologically active ingredient and a crosslinking agent in an aqueous solution of a water-soluble polysaccaride to give a mixture;

ii) subjecting the mixture to carry a crosslinking reaction under existence of a catalyst for a crosslinking reaction to give a reaction mixture; and

iii) spray-drying the reaction mixture.

19. a method for producing a microcapsule, which comprises;

i) dissolving or suspending a biologically active ingredient and a crosslinking agent in an aqueous solution of a water-soluble polysaccaride to give a mixture;

ii) subjecting the mixture to carry a crosslinking reaction under existence of a catalyst for a crosslinking reaction to give a reaction mixture; and

iii) spray-drying the reaction mixture.

20. A agricultural, pharmaceutical or fertilizal composition, which comprises a microcapsule of claim 2 and a suitable carrier.

21. A composition according to claim 20, which contains a microcapsule of claim 2, at least a biologically active ingredient which is incompatible to the biologically active ingredient in the microcapsule and a suitable carrier.

22. Use of a crosslinked product derived from a water-soluble polysaccharide for prolonged releasing biological active ingredient from a composition.

INTERNATIONAL SEARCH REPORT

Inter. ..ional Application No
PCT/JP 96/00508

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/50 A01N25/28 A61K9/56 A61K9/60 A61K9/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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Y	---	9-15,21
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X	GB,A,2 265 594 (MICRO FLO COMPANY) 6 October 1993 see page 9, line 3 - line 12; claims 1,3	1-11, 17-20,22
Y	---	12-16,21
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 1996	05.07.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Herrera, S

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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International Application No
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